# Complete Summary

## GUIDELINE TITLE

The role of neurokinin-1 receptor antagonists in the prevention of emesis due to high-dose cisplatin.

## BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Warr D, Oliver T. The role of neurokinin-1 receptor antagonists in the prevention of emesis due to high-dose cisplatin. Toronto (ON): Cancer Care Ontario (CCO); 2005 Apr 5. 27 p. (Evidence-based series; no. 12-4). [20 references]

## GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Nausea and vomiting due to chemotherapy with high-dose cisplatin

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention

### CLINICAL SPECIALTY

Oncology

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

To evaluate the role of neurokinin-1 (NK-1) receptor antagonists in the prevention of nausea and vomiting due to chemotherapy with high-dose cisplatin

### TARGET POPULATION

Adult cancer patients scheduled to receive high single doses of cisplatin delivered alone or as part of a combined chemotherapy regimen

### INTERVENTIONS AND PRACTICES CONSIDERED

Combination drug therapy including:

1. Neurokinin-1 (NK-1) receptor antagonist (aprepitant)
2. 5-hydroxytryptamine-3 (5-$HT_3$) receptor antagonist
3. Dexamethasone

### MAJOR OUTCOMES CONSIDERED

- Emesis
- Nausea
- Adverse events related to treatment
- Quality of life

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The literature was searched using MEDLINE (OVID; 1996 through August 2004), EMBASE (OVID: 1996 to August 2004), the Cochrane Library (Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse. In addition, conference proceedings of the meetings of the American Society of Clinical Oncology (1997-2004), and the European Society for Medical Oncology (1998, 2000, 2002) were searched for relevant abstracts. Article bibliographies, Internet sites, and personal files were also searched to August 2004 for evidence relevant to the guideline question.

The literature search combined disease-specific terms (neoplasms/ or cancer:.tw. or malignan:.tw. or tumour:.tw.) with treatment-specific terms (L-754,030.tw. or L-758,298.tw. or aprepitant.mp. or Emend.mp. or receptors, neurokinin-1/ or MK-869.mp. or substance P/) with search-specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, or randomized controlled trials.

### Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published reports or published abstracts of randomized controlled trials that met the following criteria:

- The reports compared aprepitant with a suitable control group (standard treatment or other novel antiemetic) in adult cancer patients receiving high-dose cisplatin.
- Results were reported for the primary outcomes of interest: emesis, nausea, adverse events related to treatment, and/or quality of life.

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also eligible for inclusion in the systematic review of the evidence.

### Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they were papers published in a language other than English.

## NUMBER OF SOURCE DOCUMENTS

Two phase III and six phase II/III double-blind randomized controlled trials, one systematic review, and one meta-analysis were identified and considered eligible for review.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

### Synthesizing the Evidence

Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Where appropriate, data on outcomes of interest are pooled across trials using a clinically relevant event or time-point. Data are pooled using Review Manager 4.0.3 (Metaview© Update Software), available through the Cochrane Collaboration (www.cochrane.org). The random effects model is generally preferred over the fixed effects model as the more conservative estimate of effect. Results are expressed as the Risk Ratio (RR) with 95% confidence intervals (CI), where an RR less than 1.0 favours the experimental treatment and an RR greater than 1.0 favours control. The number of patients needed to treat for one additional patient to benefit (NNT) is calculated using the inverse of the risk difference. Where appropriate, sensitivity analyses are conducted to determine whether particular study characteristics influence the estimate of treatment effect.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

### Disease Site Group (DSG) Consensus Process

Randomized data of cisplatin-naive patients scheduled to receive highly-emetogenic cisplatin-containing chemotherapy show a large clinical benefit in the reduction of emesis and use of rescue medication when aprepitant is added to a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist and dexamethasone. For this patient population, aprepitant is clearly beneficial and should be included as part of the standard antiemetic regimen.

The role of aprepitant in lower-dose cisplatin-based chemotherapy was considered by the Systemic Treatment Disease Site Group (DSG). There is no uniform definition of what constitutes "highly emetogenic chemotherapy". Clinical trials generally use this nomenclature to refer to chemotherapy that includes high-dose cisplatin, generally at least 70 $mg/m^2$ of cisplatin; however, lesser doses of cisplatin are still regarded as emetogenic. Indeed, the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), and the Hesketh Classification of Emetogenicity listed doses of cisplatin $\geq$ 50 $mg/m^2$ as highly emetic." In the randomized trials identified, the mean dose of cisplatin exceeded 75 $mg/m^2$ across all trials. Disease Site Group members agreed that, while the data do not directly address this issue, aprepitant as part of standard

antiemetic therapy is a reasonable treatment option in cases where the anticipated risk of emesis with lower doses of cisplatin is high.

For patients with prior cisplatin exposure, at any dose level, who have experienced emesis refractory to a 5-HT3 receptor antagonist plus dexamethasone, the Disease Site Group agreed that it is a reasonable extrapolation from the available data to recommend the addition of aprepitant as part of the standard of care, if further treatment with cisplatin is indicated.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

### External Review by Ontario Clinicians

Following review and discussion of sections 1 (clinical practice guideline) and 2 (systematic review) of the evidence-based series, the Systemic Treatment Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 of the original guideline document summarizes the draft clinical recommendations and supporting evidence developed by the panel.

### Methods

Practitioner feedback was obtained through a mailed survey of 134 medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on June 18, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Systemic Treatment DSG reviewed the results of the survey.

### Practice Guidelines Coordinating Committee Approval Process

The evidence-based series was circulated to 15 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of the 15 members returned ballots; however, two members of the PGCC, who either sit on the Systemic Treatment DSG or who were involved in the development of the

report, were not eligible to comment on the document. Five PGCC members approved the evidence-based series as written, and one member approved the report conditional on certain changes (see items 1-3 in the "Summary of Written Comments" in the original guideline document). Two members submitted comments for consideration (see items 4-6 in the "Summary of Written Comments" in the original guideline document); however, a written response by the Systemic Treatment DSG was not required.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- In the prevention of emesis due to chemotherapy with high-dose cisplatin, it is recommended that the standard of care include the neurokinin-1 (NK-1) receptor antagonist, aprepitant, in combination with a 5-hydroxytryptamine-3 ($5\text{-HT}_3$) receptor antagonist and dexamethasone.
    - This recommendation applies to patients with no prior cisplatin exposure who are scheduled to receive doses of cisplatin $\geq$70 mg/m$^2$.
    - This recommendation could also be considered for:
        - Patients with no prior cisplatin exposure who are scheduled to receive doses of cisplatin that are still considered to be emetic, but are ones that are less than 70 mg/m$^2$. With no direct evidence, a minimum cisplatin dose cannot be established.
        - Patients with prior cisplatin exposure at any dose level and emesis refractory to a $5\text{-HT}_3$ receptor antagonist plus dexamethasone. This is based upon an extrapolation of the available data.
- It is recommended that 125 mg of aprepitant be taken orally one hour prior to cisplatin, followed by a standard dose of one of the commercially available $5\text{-HT}_3$ receptor antagonists and 12 mg of oral dexamethasone administered one half-hour prior to cisplatin. In addition, 80 mg of aprepitant is taken orally every morning on days 2 to 3 along with 8 mg of dexamethasone taken on days 2 to 4.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials, one systematic review, and one meta-analysis.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Two phase III trials reported an absolute improvement in overall complete response from emesis of approximately 20% with the 125/80 mg aprepitant regimen compared with standard treatment alone. Pooled data across two phase III trials and two phase II/III trials confirm a strong treatment effect with aprepitant (relative risk=0.61; 95% confidence interval, 0.54 to 0.69; p=0.00001; number-needed-to-treat=5; 95% confidence interval, 4 to 6).
- Two phase III trials reported less nausea in patients who received aprepitant compared with standard therapy; however the difference was only significant in one trial. Pooled data across two phase III trials and three phase II/III trials confirm a significant treatment effect with aprepitant (relative risk=0.82; 95% confidence interval, 0.73 to 0.91; p=0.0004; number-needed-to-treat=8; 95% confidence interval, 6 to 20).

### POTENTIAL HARMS

Adverse events were generally reported as mild to moderate. No statistically significant differences in drug-related common or serious adverse events were reported between treatment groups in any of the randomized trials. Overall and drug-related adverse events are presented in Table 3 and commonly reported low-grade adverse events are presented in Table 4 in the original guideline document.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- The mean cisplatin dose was greater than 70 mg/m$^2$ in all the clinical trials, but it is well documented that lesser doses are still emetogenic.
- In the two phase III trials, the dose of dexamethasone was reduced by approximately 50% when compared to the control group. That was because pharmacokinetic data analyses found that aprepitant elevates dexamethasone concentrations approximately two-fold when dexamethasone is delivered orally. There are no data on the effect of aprepitant on dexamethasone levels when that glucocorticoid is given intravenously. Pharmacokinetic data with methylprednisolone suggest that aprepitant has substantially less effect on glucocorticoid plasma levels when the glucocorticoid is given intravenously.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness
Staying Healthy

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Warr D, Oliver T. The role of neurokinin-1 receptor antagonists in the prevention of emesis due to high-dose cisplatin. Toronto (ON): Cancer Care Ontario (CCO); 2005 Apr 5. 27 p. (Evidence-based series; no. 12-4). [20 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2005 Apr 5

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

### GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Ontario Systemic Treatment Disease Site Group (DSG) disclose potential conflicts of interest related to all guideline development. Potential conflicts of interest are documented by the Disease Site Group and are available for review upon request. The lead author of this guideline report has performed contract work and has acted as a consultant for the pharmaceutical company that produces aprepitant. The lead author has also been compensated by other pharmaceutical companies that are developing other neurokinin-1 (NK-1) receptor antagonists.

As is current practice for most agents in early development, all the comparative studies of the agent in question were funded by the sponsoring manufacturer of the product. Most trials indicated that the principal investigators acted as compensated consultants, and several authors of the published reports were employees of Merck and Company, Inc. Pharmaceutical involvement in clinical trials does cause concern regarding potential conflicts of interest; however, those clinical trials are typically based upon favourable pre-clinical data, are methodologically sound, are usually conducted under stringent conditions, and are also subject to external auditing from governing bodies. Having results from independently managed trials to confirm the results of pharmaceutical-sponsored studies would be preferable, but those data are often not available.

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## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of neurokinin-1 receptor antagonists in the prevention of emesis due to high-dose cisplatin: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Apr 5. Various p. (Practice guideline; no. 12-4. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on November 23, 2005. The information was verified by the guideline developer on December 13, 2005.

## COPYRIGHT STATEMENT



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